Impact of the Vial Capping Process on Residual Seal Force and Container Closure Integrity

PDA Container Closure Integrity Course, Rome

Roman Mathaes, Drug Product Services, Lonza AG

Outline

Introduction	Lab scale experiments	GMP Manufacturing	Conclusion
			
Capping, Regulatory Framework	RSF, CT, He-Leak	Large Scale capping equipment	Process parameter setting

Motivation

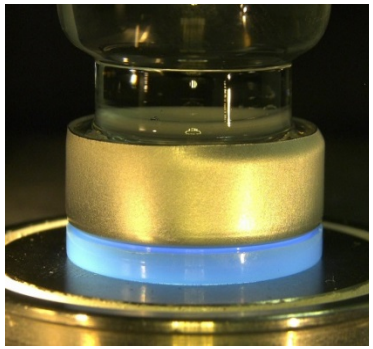
1. The capping process can impacts container closure integrity (CCI) and can cause cosmetic defects.
2. Authorities increasingly recognize the criticality the vial capping process (USP <1207.3> revision).
3. Across the clinical and commercial manufacturing sites a variety of capping techniques and packaging configurations are implemented.
4. Capping equipment independent methods are insufficiently described.

Mathaes et al., The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests, EJPB, 2015

Capping Associated Issues

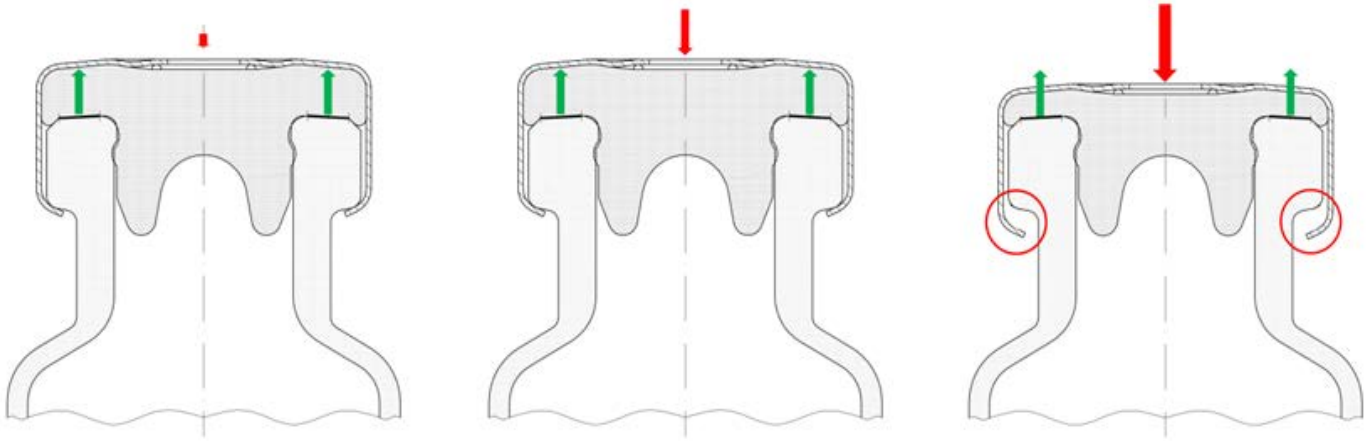
Examples of defects
Scratches on vial neck, crimp cap wrinkles, scratches on the crimp cap
Partially crimped vials
Dimpling rubber stoppers
Removal of the crimp cap upon flip-off button removal
CCI failure because of low stopper compression
Time consuming validation process
Subjective visual inspection of capped vials

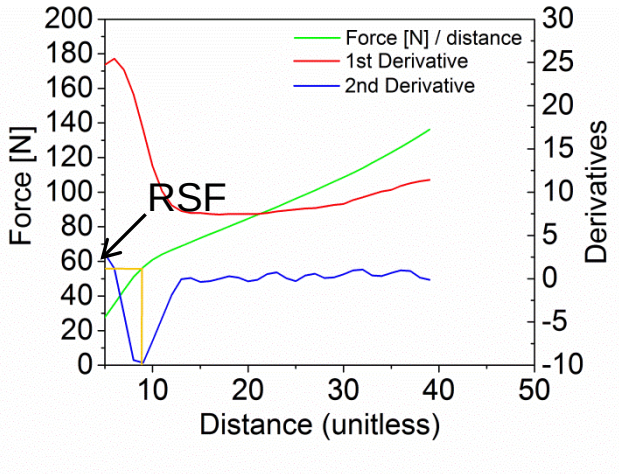
Partially crimped vials:



Dimpling:

Residual Seal Force





The RSF tester measures the force / distance curve (green line).
The RSF (56 N, yellow line) is derived from the minimum of the 2nd derivative of the force / distance curve.

Experimental Setup: Lab Scale

Vial neck	Rubber stopper	Crimp Cap
13 mm 20 mm	Serum D777-1	Datwyler
		West
	Serum D713	Datwyler
		West
	Serum West 50	Datwyler
13 mm 20 mm	Lyo D777-1	Datwyler
		West
	Lyo D713	Datwyler
		West
	Lyo West 50	Datwyler

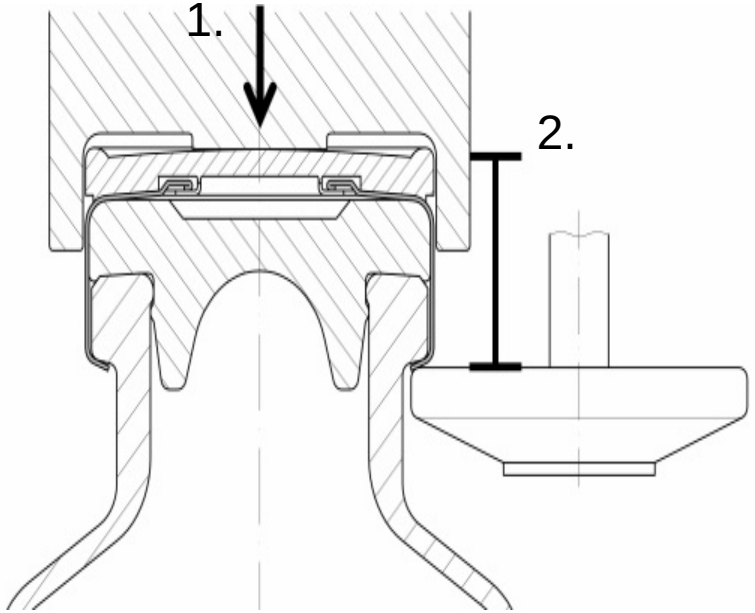
Integra West Capper:

Capping Equipment Settings

Capping equipment settings

Setting No.	Capping plate to plunger [mm]	Force [N]
1	9.19	44.48
2	8.86	44.48
3	8.48	44.48
4	8.35	75.62
5	7.98	222.41

Key capping parameters



1. Capping force
2. Capping plate height

Aim of the Study

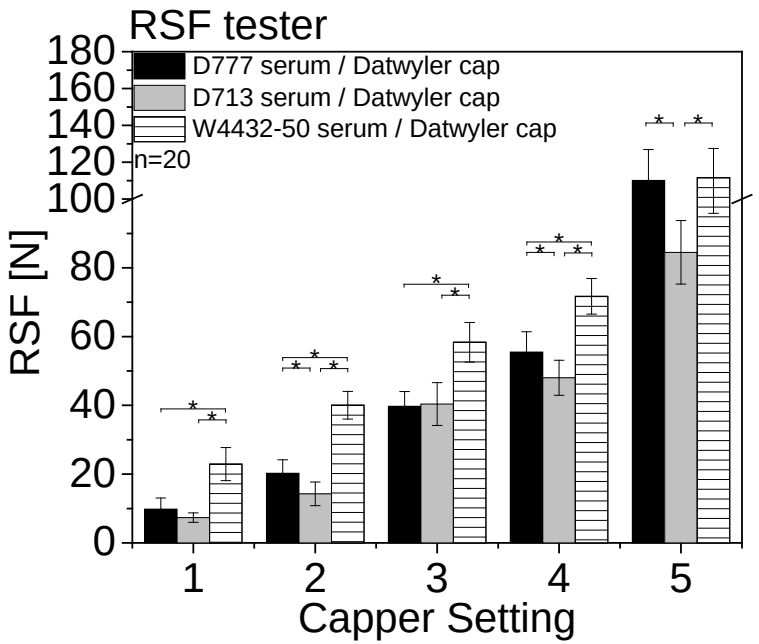
- Define and investigate key capping process parameters
- Establish a capper independent method (residual seal force (RSF) tester) to monitor the capping process
- Define a safe and robust RSF range for container closure systems (CCS)

➢ Improve the robustness of the capping process → less risk for major and minor defects

➢ Standardize capping → simplify the capping equipment validation

RSF 20 mm Neck Vials

Different rubber stopper types

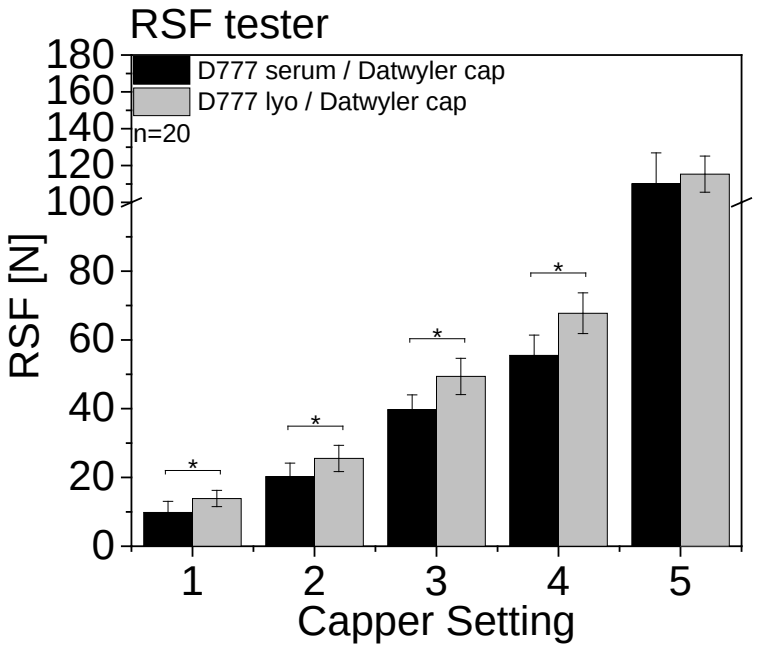


- Increased RSF with increased rubber stopper flange height (West vs. Daikyo).
- The rubber stopper shore A hardness had only a minor effect (D777 vs. D713).

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016

RSF 20 mm Neck Vials

Rubber stopper design (lyo vs. serum)

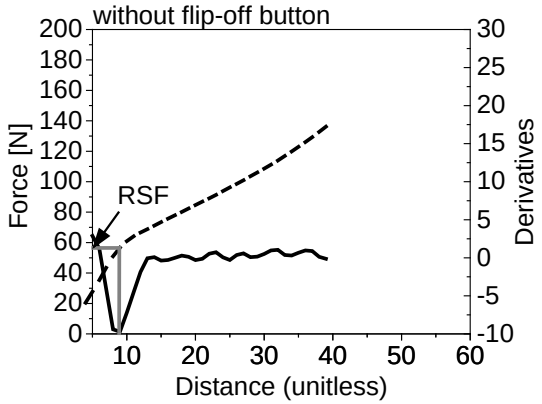


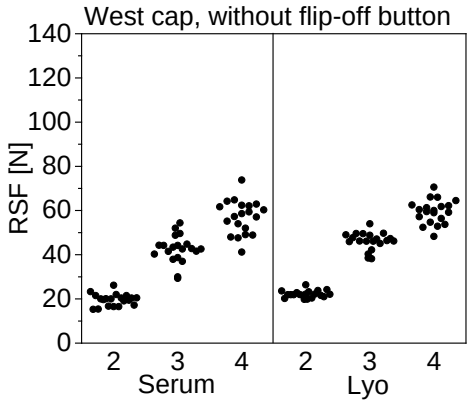
- The rubber stopper design had only a minor effect.

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016

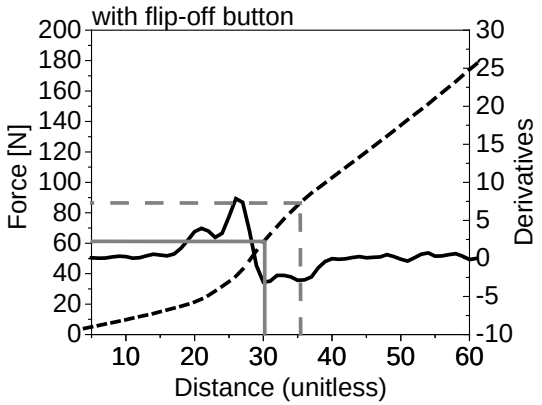
RSF 20 mm Neck Vials: Influence of the Flip-off Button

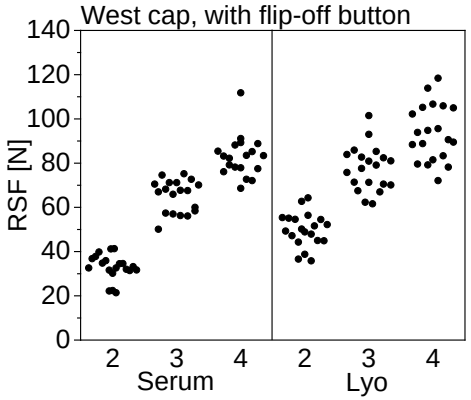
RSF without flip-off button





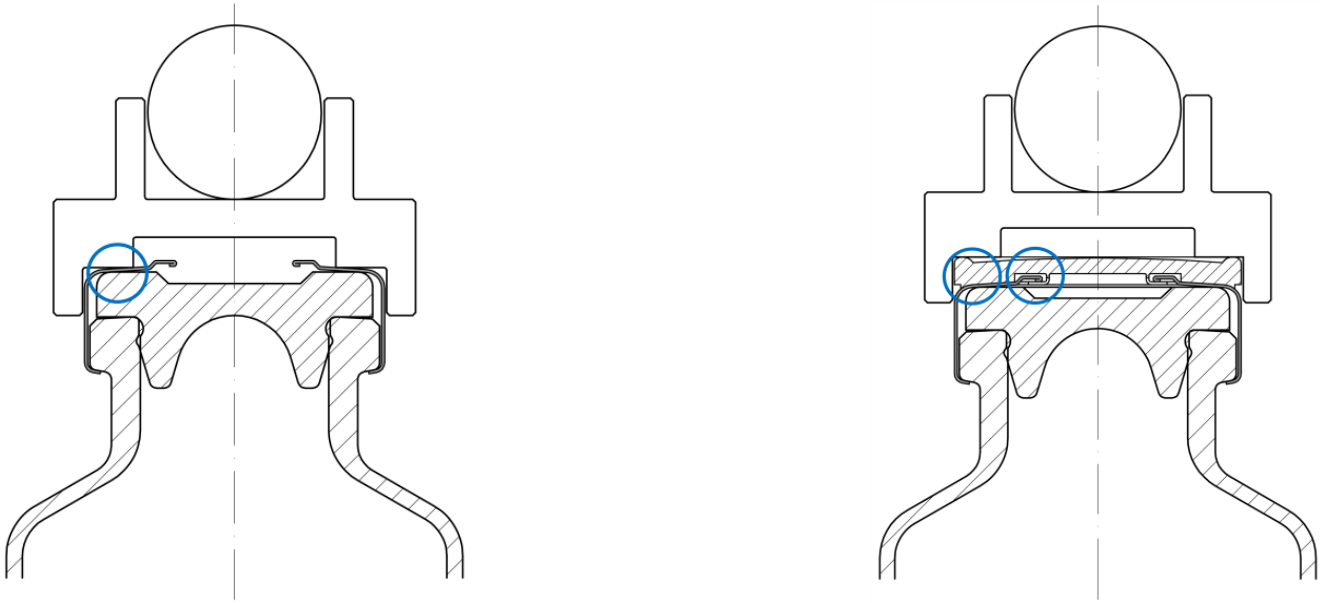
RSF with flip-off button





RSF Influence of the Flip-off Button

Measuring with flip-off button vs. without flip-off button



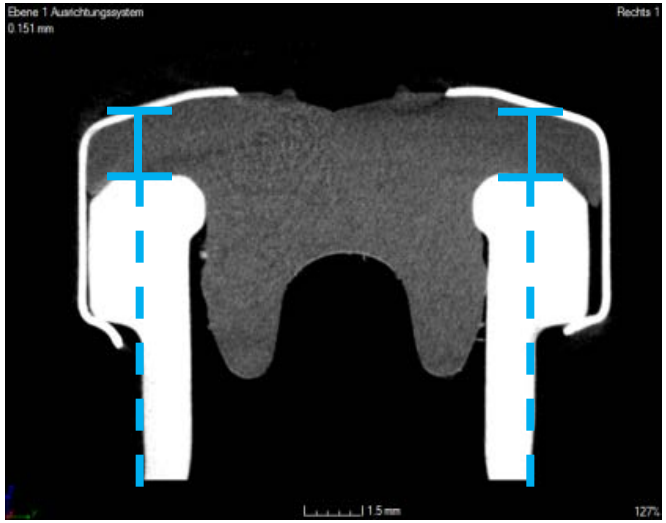
The flip-off button adds complexity to the CCS.

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016

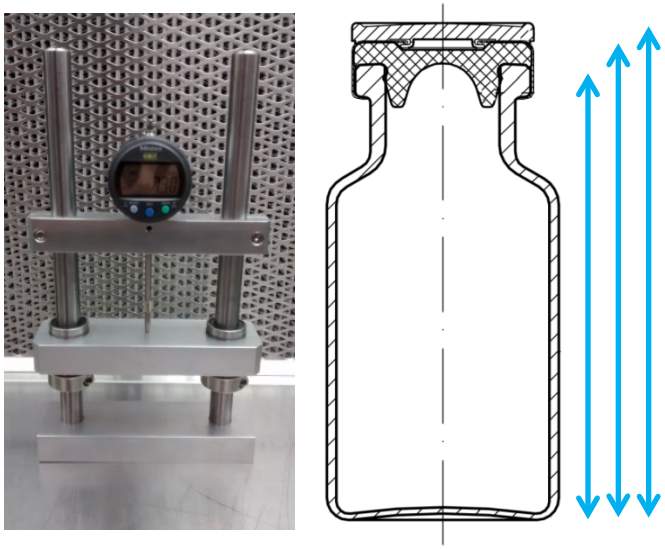
Extended characterization: Stopper Compression

Stopper compression as a function of RSF

CT measurements:



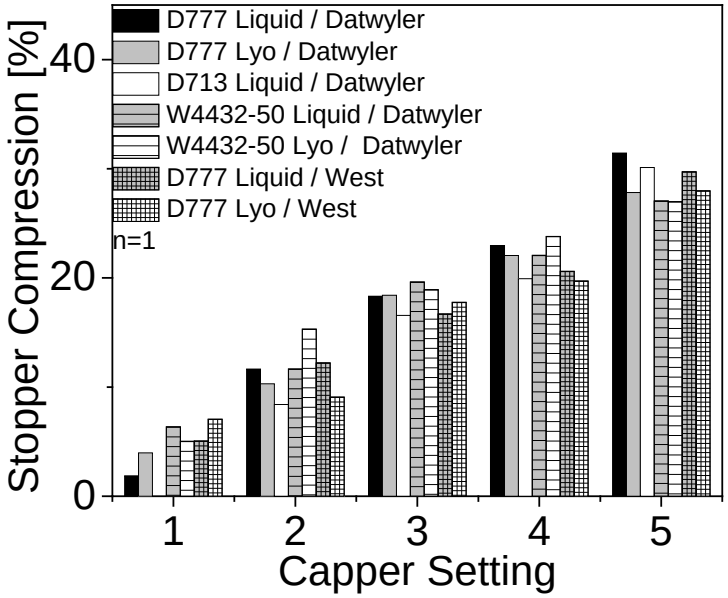
Vial height measurements:



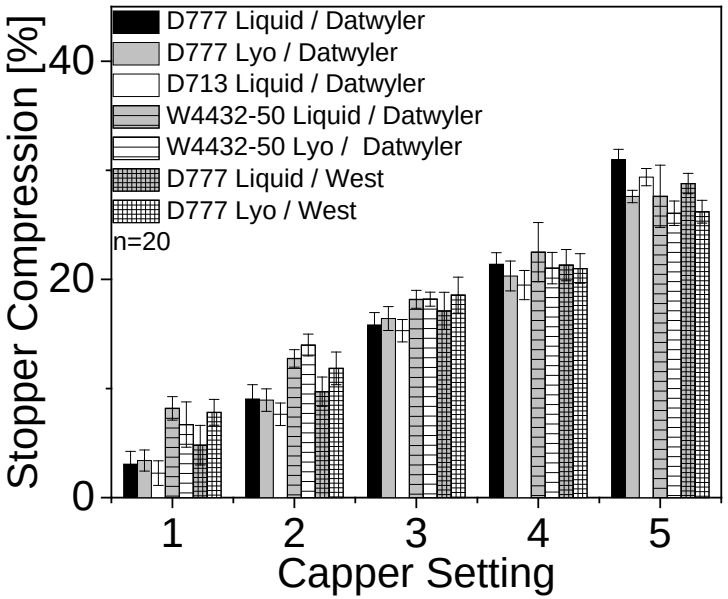
$$\text{Stopper compression} = \frac{\text{Flange height before capping} - \text{Flange height after capping}}{\text{Flange height before capping}}$$

Stopper Compression 20 mm Neck Vials

CT measurements



Vial height measurements



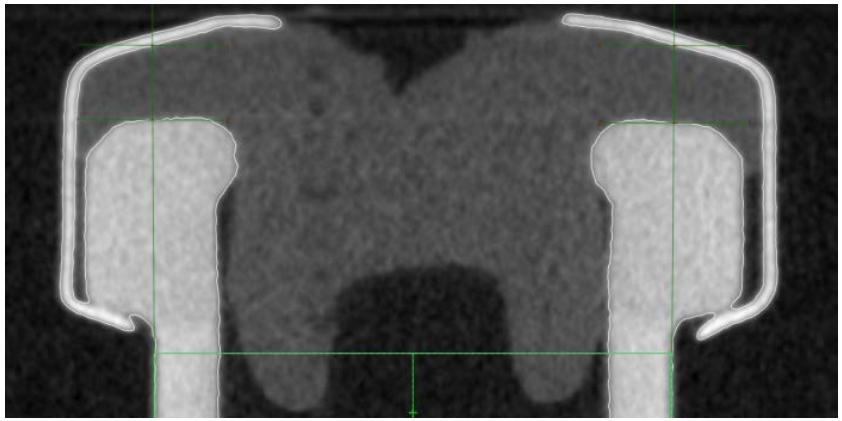
Rubber stopper compression is a function of RSF.
CT and vial height measurements showed good correlation.

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016

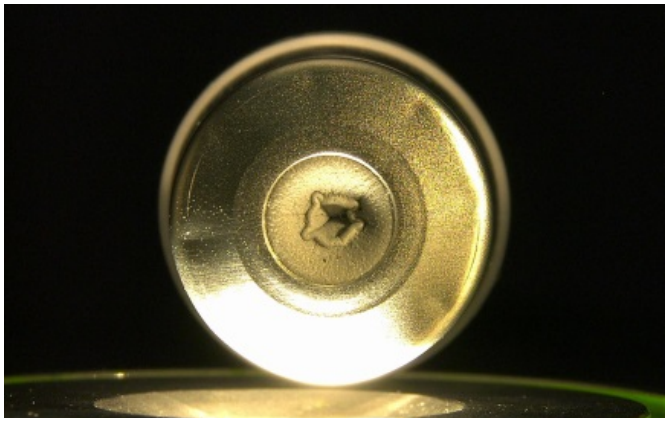
Rubber Stopper Defects

All formats were measured with CT and were visually inspected

CT measurements:



Visual inspection:



Worst case Capper setting 6, D777-1 liquid, RSF = 101 N

The soft D777-1 liquid rubber stopper showed dimpling.

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016

Defining an Adequate RSF Range for a CCS?

CCI or microorganism tightness not assured
Partially folded crimp cap

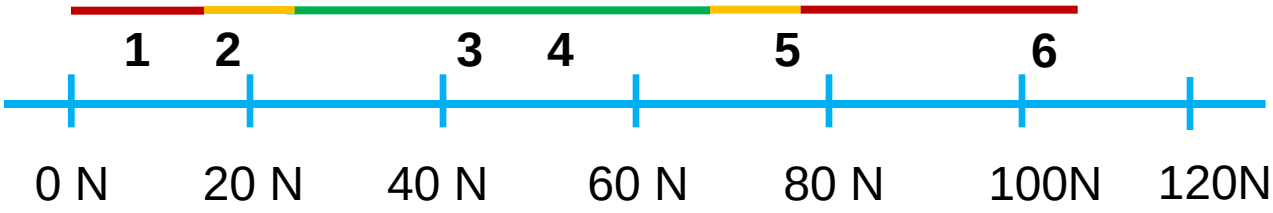
Secure RSF range

Stopper dimpling / rupture
Wrinkled crimp cap

- Vials capped with different capping equipment settings
- Measure RSF and use extended characterization methods
- Define a safety margin
- Define a secure RSF range for each CSS configuration
- Run commercial capping equipment in the secure RSF range

Example: Define an Adequate RSF Range

13 mm Neck Vial, D777-1 liquid rubber stopper, West crimp cap



- Vials capped with RSF 16 N – 101 N
- No vials showed helium leakage, vials with RSF 101 N showed dimpling
- Define a safety margin of e.g. 10 N
- Acceptable RSF range of 26 N – 66 N
- Capping equipment RSF set value 46 N

Experimental Setup: Drug Product Manufacturing

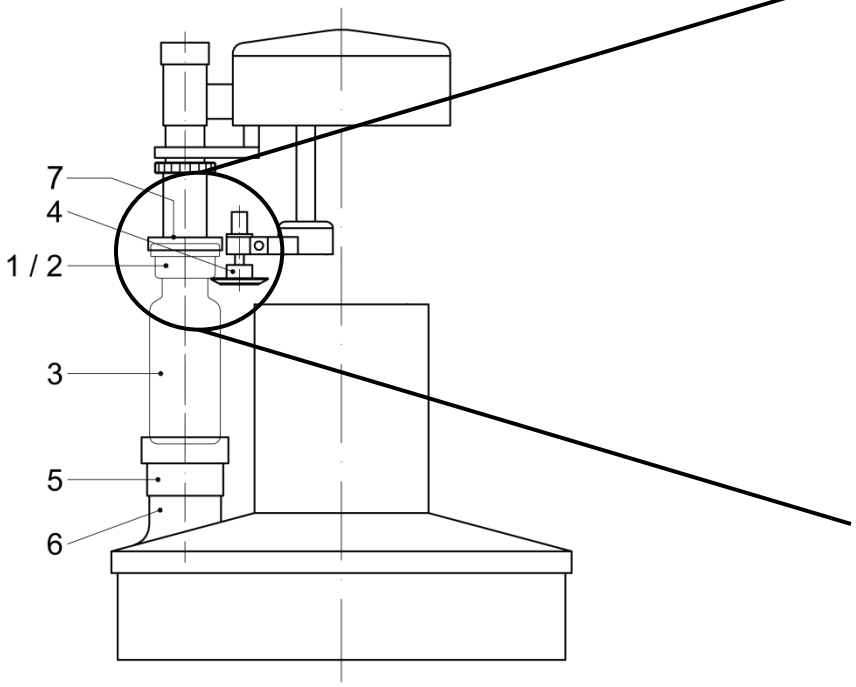
- Different process parameter
- Different formats
- Different capping equipment

Describe the key capping parameters for the commercial capper

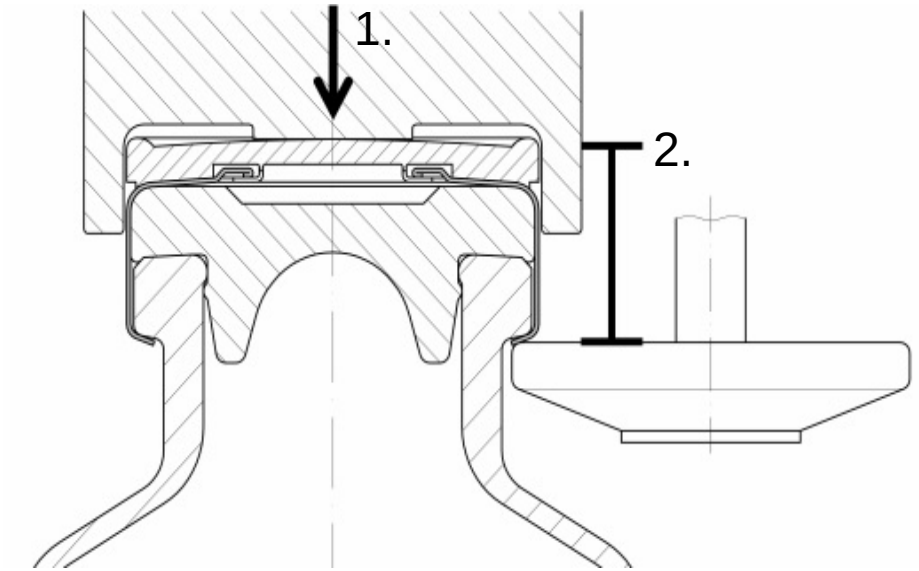
Ensure that commercially produced vials correlate to the lab scale data

Capping Process Parameters

Commercial capping equipment



Key capping parameter

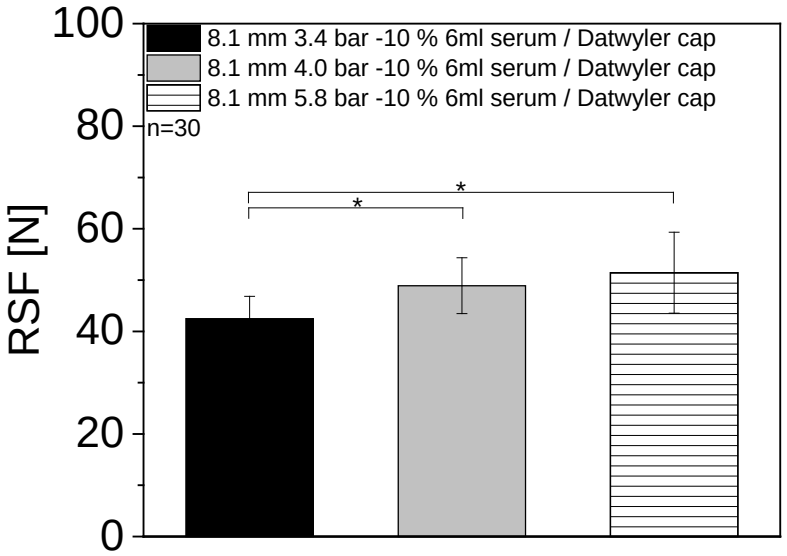


1. Capping force
2. Capping plate height
3. Rotation speed of the turntable

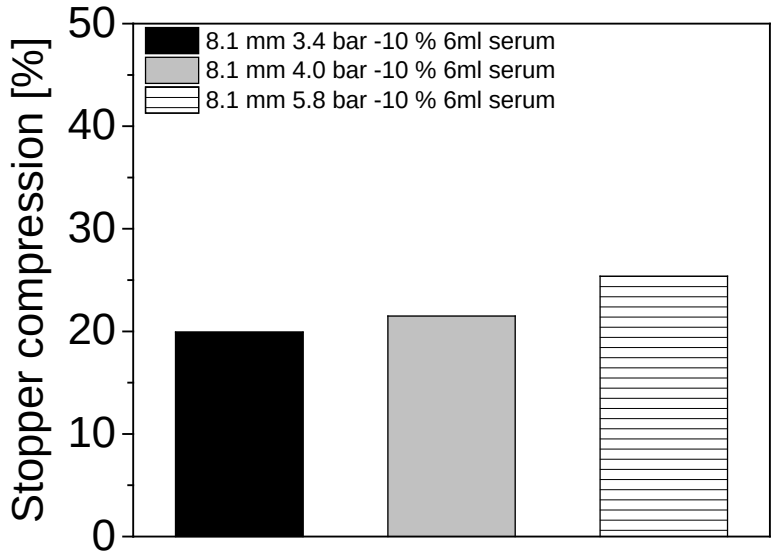
Commercial Site: 6 ml Serum Vials

Influence of the <u>capping pre-compression force</u>

RSF measurements



CT measurements



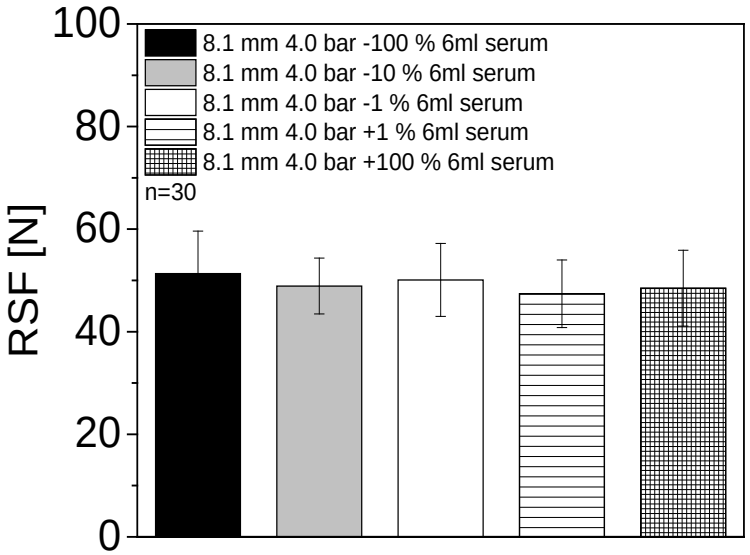
The capping pre-compression force had only a minor influencing on RSF.

Mathaes et al., Critical Process Parameters of Capping Equipment used in GMP DP manufacturing, PDA, 2016

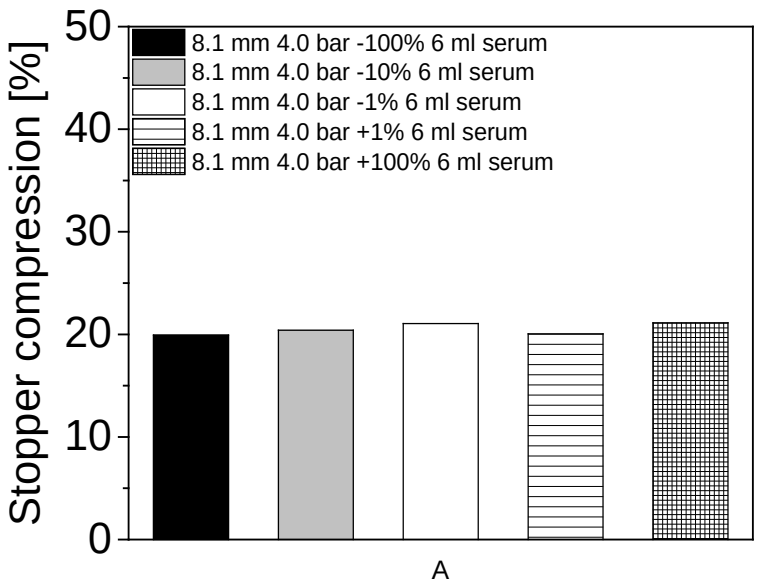
Commercial Site: 6 ml Serum Vials

Influence of the <u>rotation speed of the turntable</u>

RSF measurements



CT measurements



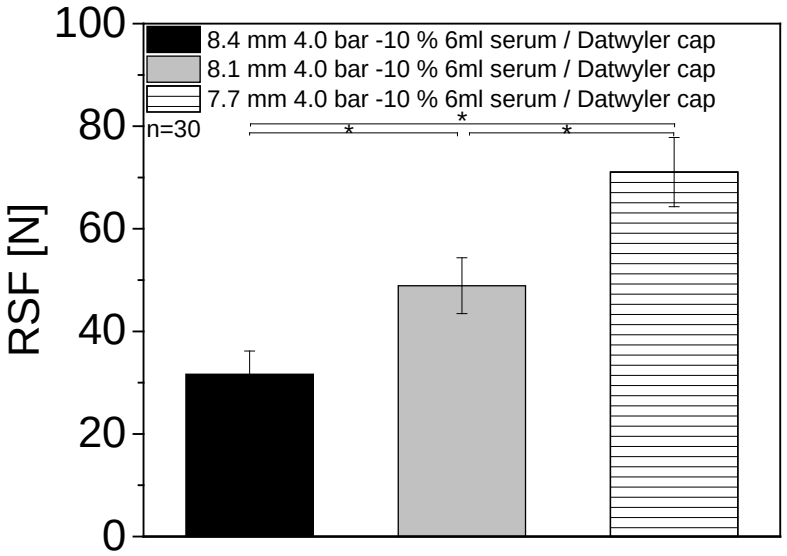
The rotation speed of the turntable had only a minor influence c RSF.

Mathaes et al., Critical Process Parameters of Capping Equipment used in GMP DP manufacturing, PDA, 2016

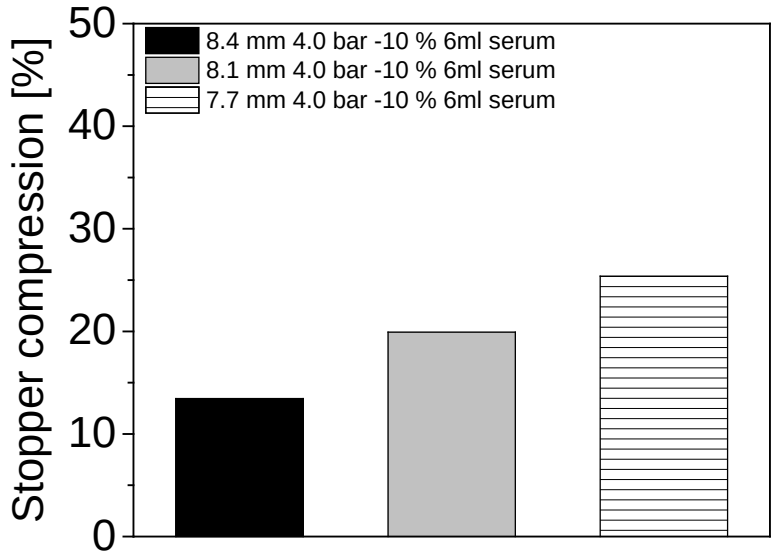
Commercial Site: 6 ml Serum Vial

Influence of the <u>capping plate-plunger distance</u>

RSF measurements



CT measurements



The capping plate-plunger distance has a major influence on RSF.

Mathaes et al., Critical Process Parameters of Capping Equipment used in GMP DP manufacturing, PDA, 2016

Conclusions

- RSF technology is a reliable and precise tool to characterize the quality of the capped product in dependence of the capping process parameters, independent of the used CCS and capping equipment.
- Capping pre-compression force is not the only RSF influencing capping process parameter.
- Stopper compression can be measured by CT or vial height measurements and is a function of RSF.
- A secure RSF range can be defined.

Lonza: Drug Product Services

Hanns-Christian Mahler

Atanas Koulov

www.lonza.com/drugproduct
DrugProduct@lonza.com

References

1. Mathaes, R., et al., The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests, EJPB, 2015

2. Mathaes, R., et al., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016

3. Mathaes, R., et al., Critical Process Parameters of Capping Equipment used in GMP DP manufacturing, PDA, 2016

4. Mathaes, R., et al., The Pharmaceutical Capping Process - Correlation between Residual Seal Force, Torque Moment and Flip-off Removal Force, PDA 2016